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Original Article

Neurobehavioral and autonomic alterations in adults with obstructive sleep apnea

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is associated with sympathetic hyperactivity, excessive nocturnal sweating, sleepiness, and neurobehavioral cognitive alterations. However, it is not well known if cognitive consequences of OSA are independent from autonomic alterations. Thus, we assessed the association between polysomnographic, autonomic, and cognitive tests performance in OSA patients.
Methods: Fifty eight OSA patients (53 male) were administered with questionnaires assessing demographic, Epworth, Beck Depression Inventory, Syndrom Kurz test (SKT), Trail Making part B (TMT-B), and Frontal Assessment Battery (FAB) tests. Spectral analysis of heart rate variability (HRV) and night sweating symptoms (NSwS) score were used to assess autonomic function.
Results: Global cognitive function (SKT) was normal in mild-moderate (M-OSA) and severe (S-OSA) patients. In S-OSA patients AHI was correlated with TMT-B ($r = 0.30$ $P < 0.05$) and with FAB ($r = -0.31$ $P < 0.05$). Oxygen desaturation was correlated with TMT-B ($r = -0.45$ $P = < 0.001$) and FAB ($r = 0.29$ $P = < 0.05$). Sympathetic overactivity was correlated with oxygen desaturation: HRV ($r = -0.39$ $P < 0.05$) and NSwS score ($r = -0.49$ $P < 0.01$), but HRV and NSwS score were not correlated with TMT-B and FAB.
Conclusion: Frontal cognitive dysfunction and predominance of sympathetic drive occur in OSA patients. Abnormal frontal cognitive function and sympathetic hyperactivity were related to oxygen desaturation, but not between each other. We conclude that neurobehavioral changes and autonomic imbalance in OSA patients take place independently from each other, suggesting different pathophysiological pathways.

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1. Introduction

The OSA syndrome is associated with significant neurobehavioral alterations including daytime sleepiness, fatigue, depressed mood, deficits in attention, executive function, verbal and visuoespatial memory [1–3]. Functional brain imaging in OSA patients [4,5] and studies in animal models had shown selective neuronal injury [6], but global intellectual dysfunction is less frequent in OSA patients [3]. In addition, OSA is recognized as an independent risk factor for systemic hypertension and other cardiovascular diseases [7,8]. It has been shown that chronic intermittent hypoxia (CIH), the main feature of OSA, produces oxidative stress, inflammation, and sympathetic hyperactivity, which led to endothelial dysfunction and hypertension [9–12]. In OSA patients autonomic alterations are characterized by enhanced sympathetic activity [13], reduced efficiency of the baroreflex sensitivity and changes in heart rate variability (HRV) [14], suggesting preponderance of the sympathetic drive and elevated urinary and plasma catecholamines [15]. Elevated skin sympathetic activity related to nocturnal sweating is also present in OSA patients [16].

Among potential pathophysiological mechanisms that may contribute to produce neurocognitive deficits, the CIH-induced sympathetic overactivity may contribute to evoke inflammation in organs and vascular beds. The humoral and vascular dysfunction may also be responsible for the altered cerebral perfusion [3]. In the present study, we sought to assess the cognitive impairment and sympathetic dysfunction in untreated OSA patients and establish if there is any association between frontal cognitive impairment, polysomnographic variables, HRV, and nocturnal sweating.

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2. Methods

2.1. Patients

Fifty-eight consecutive patients (53 male) referred to the Sleep Center of the Department of Neurology, Pontificia Universidad Católica de Chile, for suspected sleep apnea were recruited. The research was conducted in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the School of Medicine, Universidad de Valparaiso. The inclusion criteria were polysomnographic (PSG) diagnosis of OSA, age between 15 and 60 years old and complete high school education. The exclusion criteria were Parkinsonism, dementia, stroke, epilepsy, brain injury, drug or alcohol abuse, or drug treatments, which may interfere with autonomic function. Each patient gave written informed consent.

2.2. Polysomnography evaluation

Patients underwent nocturnal video-polysomnography. Sleep and physiological variables were monitored with a RESPIRONIC Alice 5 Diagnostic Sleep System (Philips Respironics, Amsterdam, The Netherlands). A ten-channel recording montage (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2) was used to measure EEG activity. Left and right electrooculography, electrocardiography, and sub mental electromyography (EMG), oronasal airflow (using a thermal sensor and nasal pressure transducer), body position, thoracic and abdominal excursion (inductance plethysmograph), oxygen arterial blood saturation (SaO_2) measured with finger pulse oxymetry, left and right leg movement (EMG channel), and sound recorder was used.

Apnea was defined as a drop in the peak thermal sensor excursion by ≥90% of baseline, for at least 10 s and hypopnea as a drop in the nasal pressure signal excursions by ≥30% of baseline, for at least 10 s, followed by ≥4% desaturation from pre-event baseline [17]. Grade of OSA severity were defined as mild: 5–15 AHI, moderate: >15–30 AHI, and severe >30 AHI.

2.3. Neurobehavioral evaluation

After giving their informed consent, patients were administered with a questionnaire assessing demographic characteristics, the Epworth Sleepiness Scale [18], and the Beck Depression Inventory [19]. Then the patients were subjected to the Syndrom Kurz (SKT), the Trail Making-B (TMT-B), and the Frontal Assessment Battery (FAB) tests. The session lasted about 60 min.

The SKT was used to detect global cognitive impairment. The test consisted of nine subtest battery, naming of 12 pictured objects and 12 numerals, immediate and delayed recall of pictured objects, recognition of previously viewed pictures, rapid counting of target stimuli and symbols embedded in a background of distracter stimuli, arranging and replacement of stimulus blocks according to numerals painted on them, and a reversal naming task in which two letters of the alphabet are responded to by naming the other. SKT measures language fluency, praxis, recall and recognition memory, and attention-concentration. Score: normal cognitive function ≤4, severe dysfunction >23 [20].

The TMT-B, measures attention, visual scanning, divided attention, and executive function. Scoring is expressed in seconds required for completion of each of the two parts of the test [21].

The FAB is used to distinguish fronto-temporal dementias from Alzheimer's disease. The test consisted of 6 subsets to measure conceptualization and abstract reasoning, verbal fluency, motor programming, resistance to conflicting instructions, inhibitory control, and environmental autonomy. Each subtest is scored from 3 to 0, for a maximum score of 18. Normal score is ≤12, and severe frontal dysfunction is the maximum score [22].

2.4 Autonomic nervous system evaluation

2.4.1. Heart rate variability (HRV)

Multi-lead electrocardiogram (ECG) was continuously acquired at 1 kHz during PSG. HRV analysis was conducted according to standard guidelines [23]. The ECG signal was exported for analysis using the HRV module of the Lab Chart-Pro analysis software (AD Instruments, Sydney, Australia). Frequency domain analyses were performed in 10-min ECG segments. The R-R wave detection was performed using the maximum after threshold method and artifacts were manually removed from the tracings. The remaining normal-to-normal R-R intervals were used for further analysis. Spectral analysis was performed using a Fast Fourier Transform algorithm with a spectrum size of 512 points, applying a Hann window with 1/2 overlap. The spectrum of R-R intervals was assessed using the following frequency bands: very low frequency: DC-0.04 Hz; low frequency (LF): 0.04–0.15 Hz; and high frequency (HF): 0.15–0.4 Hz in the frequency domain. HF power reflects the activity of parasympathetic nervous system activity, whereas LF power reflects a combination of sympathetic and parasympathetic activity [23].

2.4.2. Sweating symptoms

Patients were asked to complete a questionnaire on sweating, modified from Swinn et al. [24]. NSwS score includes questions regarding the night sweating occurrence: change night wear/bed clothes due to sweating, disturbed sleep and awakenings due to sweating. The frequency of different sweating symptoms was scored: 0 = no sweating, 1 = less than one episode during 1 week, and 2 = more than two episodes per week.

2.5. Statistical analysis

Data were expressed as mean ± SEM. The demographic characteristics and polysomnographic data were analyzed with the chi-square test for categorical variables and the Mann–Whitney test for continuous variables. Spearman's correlation coefficient (r) was used to study the univariate association between TMT-B, FAB, SKT, BMI, age, Epworth, AIH, SaO_2, micro-awakenings, LF, HF, LF/HF ratio, and nocturnal sweating. All analyses were done with the statistical significance set at $P < 0.05$.

3. Results

3.1. Baseline characteristics

The demographic and polysomnographic characteristics of the OSA patients are shown in Table 1. The mean age was 45.8 ± 9.3 years

Table 1
Demographic and polysomnographic values of OSA patients.

OSA severity	M-OSA (23)	S-OSA (35)	Total (58)	*P*
Age (years)	41.2 ± 8.8	48.9 ± 8.5	45.8 ± 9.3	0.001
Male	91.3%	91.4%	91.4%	
Female	8.7%	8.6%	8.6%	
BMI (kg/m^2)	27.8 ± 3.9	29.5 ± 5.7	28.6 ± 4.7	0.015
Epworth	12.6 ± 5.0	13.6 ± 5.6	13.2 ± 5.4	0.460
Diabetes	0%	2.9%	1.7%	
Hypertension	13.0%	37.1%	27.6%	0.071
SaO_2 %	86.0 ± 9.0	75.0 ± 15.0	80.0 ± 13.0	0.001
Without desaturation	13.0%	0%	5.3%	0.001
Mild	43.5%	17.1%	27.6%	0.001
Moderate	34.8%	31.4%	32.8%	0.001
Severe	8.7%	51.4%	34.5%	0.001
Micro-awakenings	19.2 ± 12.8	50.3 ± 31	35.4 ± 30.8	0.001

Values are mean ± SD. BMI, body mass index; AHI, Apnea–hypopnea index, SaO_2% minimal arterial oxygen saturation. *P*, M-OSA vs. S-OSA.

and male patients predominated (91.4%). According to the PSG evaluation, patients were classified in two groups: a group of 23 patients with mild-moderate OSA (M-OSA, AHI = 18.1 ± 13.2) and a group of 35 patients with severe OSA (S-OSA, AHI = 55.3 ± 32.1). The mean Epworth scores were not significantly different between the M-OSA and S-OSA patients. Mean age and BMI were higher in the S-OSA group, but HTA and diabetes incidence were not different ($P > 0.05$).

3.2. Neurobehavioral and PSG findings

The mean score for the SKT in the 58 patients was 2.0 ± 2.0, without significant differences between the M-OSA and S-OSA groups. Note that values considered abnormal are >4 [21]. The mean TMT-B and FAB scores for all OSA patients were 64.0 ± 28.0 and 16.0 ± 2.0, respectively. Both the TMT-B and FAB tests showed a significantly worse outcome in the severe OSA group (see Table 2).

The Beck mean score for the 58 patients was 7.9 ± 4.8, and we did not find differences between both mild and severe OSA groups (Table 2). The depression percentage was similar in both M-OSA and S-OSA groups.

Table 3 shows the significant correlation coefficients between the frontal cognitive tests TMT-B, FAB and polysomnographic variables in severe OSA patients. TMT-B was significantly associated with SaO_2 ($r = –0.45$, $P < 0.001$) and AHI ($r = 0.30$, $P < 0.05$), but not with micro-awakenings ($r = 0.24$, $P > 0.05$). FAB was significant associated with SaO_2 ($r = 0.29$, $P < 0.05$), AHI ($r = –0.31$, $P < 0.05$) and micro-awakenings ($r = –0.28$, $P < 0.05$). It is worth noting that both the TMT-B and FAB scores were not associated with the Epworth score since the correlation coefficients with TMT-B was $r = 0.14$ ($P > 0.05$) and with FAB $r = –0.15$ ($P > 0.05$).

3.3. Autonomic evaluation

The analysis of HRV spectral indexes in severe OSA patients showed a ratio of LF to HF frequency power (LF/HF) of 3.93 ± 0.75, with predominance of the LF band (68.14 ± 2.96 n.u.) and a reduced of the HF band (27.71 ± 2.95 n.u.). LH/HF ratio did not show correlation with age ($r = –0.09$, $P > 0.05$) and BMI ($r = 0.20$, $P > 0.05$), but was associated with NSwS score ($r = 0.42$. $P = 0.031$). Night sweating occurrence was found in 54% of the severe OSA patients. Change night wear or bed clothes due to sweating occurred in 11% of these patients, and disturbed sleep and awakenings due to sweating in 19%.

Table 2
Cognitive tests and depression in OSA patients.

OSA severity	M-OSA (23)	S-OSA (35)	Total (58)	*P*
SKT	2.0 ± 2.0	2.0 ± 3.0	2.0 ± 2.0	0.609
TMT-B	56.0 ± 22.0	74.0 ± 54.0	64.0 ± 28.0	0.031
FAB	16.0 ± 2.0	15.0 ± 2.0	16.0 ± 2.0	0.028
Beck	8.6 ± 5.1	7.4 ± 4.6	7.9 ± 4.8	0.370
Depression	30.4%	25.7%	27.6%	0.694

Table 3
Correlation between frontal cognitive tests TMT-B and FAB with polysomnographic variables in severe OSA patients.

	r	*P*
TMT-B		
AHI	0.30	0.021
Micro-awakenings	0.24	0.069
SaO_2	–0.45	0.001
FAB		
AHI	–0.31	0.020
Micro-awakenings	–0.28	0.032
SaO_2	0.29	0.032

Table 4
Correlations between sympathetic tests (LF/HF ratio, NSwS score), cognitive dysfunction and PSG variables, in severe OSA patients.

	LF/HF ratio		NSwS score	
	r	*P*	*r*	*P*
SKT	–0.23	0.145	0.08	0.329
TMT-B	0.20	0.181	0.23	0.105
FAB	0.09	0.337	0.02	0.456
AHI	0.25	0.125	0.14	0.220
SaO_2	–0.39	0.031	–0.49	0.004

3.3.1. Autonomic, neurobehavioral and PSG association

In the severe OSA patients the NSwS score was correlated with the Epworth ($r = 0.43$, $P < 0.05$) and with SaO_2 ($r = –0.49$, $P < 0.01$), but not with the Beck depression score ($r = 0.22$, $P = 0.108$). A significant association between SaO_2 and sympathetic related variables was found in severe OSA patients. Indeed, SpO_2 was correlated with LH/HF ($r = –0.39$, $P < 0.05$), and NSwS ($r = 0.42$, $P > 0.05$). However, the LH/HF and NSwS score were not associated with SKT, TMT-B and FAB (Table 4).

4. Discussion

The main findings of this study were that frontal cognitive and sympathetic alterations in OSA patients were independently correlated with arterial blood oxygen desaturation, but no association was found between sympathetic and cognitive dysfunction. We found that severe OSA patients had lower scores on executive cognitive function tests compared with the mild/moderate OSA group. On the contrary, we did not find any significant difference in terms of global cognitive function between the mild/moderate OSA and severe OSA groups. It has been reported that increasing age, obesity, hypertension, diabetes mellitus cerebrovascular disease, and ApoE4 positivity are risk factors for cognitive dysfunction in OSA [3]. However, we did not find significant influence of age and BMI in the cognitive outcomes. Indeed, severe OSA patients had a mean age significantly higher than the group of M-OSA. We did not attribute these differences to the level of alert or mood of patients, since no significant differences in the level of subjective sleepiness (Epworth score) or the presence of depressive symptoms (Beck index) was found between the two OSA groups. It has been reported that OSA patients with depressive symptoms presented increased selective brain injury in areas related with cognitive and autonomic regulation [25]. We used the Beck Depression Inventory to assess the presence of depressive symptoms in our study population. The percentage of patients with depressive symptoms was 30.4% in M-OSA and 25.7% in S-OSA. Moreover, we did not find that depressive symptoms were neither associated with cognitive or autonomic impairment in OSA patients. Then, our data suggested that depression was not associated with neurobehavioral and/or autonomic imbalance. However, we cannot rule out that specific brain injuries could be associated with cognitive impairment and sympathetic hyper-activity in OSA. Further studies need to be done to address the contribution of selected brain injuries and neurobehavioral and autonomic function in OSA.

We found a significant inverse correlation between performance on tests of executive function and the degree of nocturnal hypoxemia, but not with the fragmentation of sleep (micro-awakening). This is consistent with previous studies, which found that frontal cognitive impairment was related to the severity of the nocturnal hypoxemia [26]. In a community study, Yaffe et al. [27], found that hypoxemia was strongly associated with a high risk of

cognitive impairment in OSA elderly women. Other studies found an independent association between hypoxemia and the decline of executive function [28]. It is worth noting that the treatment with continuous positive airway pressure (CPAP) during OSA improves cognitive and brain grey matter functional images [29]. Thus, it is plausible that CPAP treatment improves cognitive function by correcting sleep fragmentation, hypoxemia, and autonomic dysfunction.

The non-invasive spectral analysis of HRV showed that severe OSA patients had an increased ratio of low (LF) to high frequency (HF) band power, with a relative predominance of the LF band and a reduced contribution of the HF band, suggesting preponderance of the sympathetic drive [14]. The predominance of the sympathetic control of HRV was not associated with age, BMI or diurnal somnolence. In addition, our results showed that frontal cognitive dysfunction was not related with the sympathetic overactivity, measured as changes in HRV [16] and excessive nocturnal sweating [16]. Recently, Arnandottir et al. [30], proposes a possible role of frequent nocturnal sweating as a marker for untreated sleep apnea. Indeed, one-third of adults with OSA have excessive nocturnal sweating, three times more than comparable adults without OSA. However, we cannot preclude a contribution of the enhanced sympathetic activity on the progression of cognitive dysfunction. Indeed, it is possible that the enhanced sympathetic activity may play an interactive role on the potential mechanisms that could induce cognitive dysfunction in OSA. It is well known that exposure to intermittent hypoxemia leads to oxidative stress, inflammation, and sympathetic hyperactivity, all of them strongly associated with endothelial dysfunction [3]. Then, it is plausible that the brain microvascular function is impaired in OSA patients with sympathetic hyper-activity. Future studies are needed to address the contribution of brain endothelial function in the development of neurobehavioral disturbances in OSA. A limitation of our study is that we assessed autonomic dysfunction using HRV analysis and a sweating questionnaire; we did not include clinical cardiovascular autonomic tests, urinary neurotransmitter identification or functional images. Nevertheless, it has been shown that HRV correlates with urinary norepinephrine (NE) levels, a well-used systemic index of sympathetic activation. Recently Kheirandish-Gozal et al. [31], reported selective overnight central neurotransmitters alterations in children with OSA and cognitive dysfunction, including reduced β-phenyletylamine and taurine with increased GABA, while NE did not show a significant elevation. These results suggest that in children with OSA, cognitive impairment is not associated with sympathetic activation since NE levels are not significantly different. Our results showing no correlation between HRV and cognitive function in adults with OSA also supports this notion.

Since we found an association between frontal cognitive dysfunction or sympathetic overactivity with AIH and the oxygen desaturation in the severe OSA patients, it is plausible that our findings were the result of a simply severity effect of OSA. If the cognitive and sympathetic alterations were merely a sign of the OSA severity, we should expect a high positive correlation between both function. However, the frontal cognitive dysfunction found in the severe OSA group was not correlated with the sympathetic overactivity, indicating a lack of correlation between both effects. In addition, we found a similar global cognitive function between the mild/moderate OSA and severe OSA groups, suggesting that the findings observed here are not simply effects of the severity.

5. Conclusion

In severe OSA patients, frontal cognitive dysfunction and sympathetic overactivity were associated with nocturnal hypoxemia. However, frontal cognitive dysfunction was not correlated with sympathetic overactivity studied by power spectrum HRV and sweating score. Studies that combine autonomic and cognitive dysfunction in different age population could disclose a possible temporal association.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.05.030.

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